[13704/2]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Ian R. Doyle *et al.*
Serial No.	:	09/486,703
Filed	:	June 27, 2000
For	:	A METHOD OF DIAGNOSIS
Examiner	:	Patricia A. Duffy, Ph.D.
Art Unit	:	1645

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DECLARATION OF GUY B. MARKS UNDER 37 C.F.R. § 1.132

I, Guy B. Marks, residing at 19 Melody Street, Coogee, New South Wales, Australia 2034, hereby declare the following:

1. A copy of my *curriculum vitae* is attached hereto as Exhibit A.

2. I earned a Bachelor of Medical Science degree in 1980 and a Bachelor of Medicine, Bachelor of Surgery (with Honors) in 1981, both from the University of New South Wales. I earned a Doctor of Philosophy degree from the University of Sydney in 1993.

3. I have 28 years of experience as a practicing physician in Australia, and my current positions are National Health and Medical Research Council (NHMRC) Practitioner Fellow and Head, Epidemiology Group, Woolcock Institute of Medical Research (New South Wales, Australia), and Senior Staff Specialist Physician, Department of Respiratory Medicine, Liverpool Health Service (Liverpool, Australia). I was made a Fellow of the Royal Australasian College of Physicians in 1989 and a Fellow

of the Faculty of Public Health Medicine of the Royal Australasian College of Physicians in 1997.

4. I have read and understand the above-identified application, the pending claims in that application as filed on October 31, 2007, the Office Action dated July 3, 2008, the Office Action dated April 30, 2009, and Doyle *et al.* ("Surfactant as a Marker of Disease Severity in Critically Ill Patients with Respiratory Failure," Advances in Critical Care Testing, Eds. Muller and McQueen, Springer-Verlag Telos, January 1997, pp. 151-152) as cited therein.

5. In the Office Action dated July 3, 2008, claims 51-64 were rejected under 35 U.S.C. § 102(b) as being anticipated by Doyle *et al.*, and these claim rejections were maintained in the Office Action dated April 30, 2009. The Office Action dated July 3, 2008 states that "Doyle *et al.* teach measuring SpA and SpB to screening for increases in a variety of patients including ventilated patients with no evidence of cardiorespiratory disease and screening for normal individuals (see page 152, Table 1) in sera (i.e. the instant blood) and the comparison of normal to other diseases. The 'asymptomatic to lung damage or wherein the clinical diagnosis of lung damage in the mammal cannot otherwise be confirmed without the aid of one or more invasive procedures' is seen to meet this limitation as instantly claimed because the ventilated patients had no evidence/symptoms of cardiorespiratory disease and is also evidence of disease and 'during a period in which the onset of lung damage cannot otherwise be confirmed without the aid of one or more invasive procedures.'... Further, the screening of 'normal individuals' also meets the limitation of the claims, since these individuals would not be exhibiting a symptom specific to lung damage.... As such, the patient populations tested by Doyle [*et al.*] meet the limitations of the patient population claimed herein." (Office Action dated July 3, 2008, pages 2-3).

6. Doyle *et al.* is entitled "Surfactant as a Marker of Disease Severity in Critically Ill Patients with Respiratory Failure," and it discloses the evaluation of plasma levels of surfactant protein A (SP-A) and surfactant protein B (SP-B) in such critically ill patients with respiratory failure. These critically ill patients in Doyle *et al.* suffered from either acute cardiogenic pulmonary oedema (APE) or acute respiratory distress syndrome (ARDS), and the SP-A and SP-B plasma levels for such critically ill patients were compared to those of "normal individuals (controls)" and "ventilated patients with no

evidence of cardiorespiratory disease (OD)." However, based on the disclosure of Doyle *et al.*, it is unclear as to the extent that the "normal individuals (controls)" and the "ventilated patients with no evidence of cardiorespiratory disease (OD)" were screened prior to their enrollment in the study. That is, the "normal individuals (controls)" and the "ventilated patients with no evidence of cardiorespiratory disease (OD)" apparently did not have APE or ARDS; however, Doyle *et al.* does not disclose what further level of detail was employed in the screening process. Upon reading Doyle *et al.*, one of ordinary skill in the art would expect that the "normal individuals (controls)" and the "ventilated patients with no evidence of cardiorespiratory disease (OD)" disclosed therein would likely not have overt evidence of any cardiorespiratory disease or other similar condition likely to influence the measurements under study, but the precise physical characteristics of the individuals in the normal or OD groups is not conclusively apparent.

7. The method claimed in the above-identified application, as currently recited in independent claim 51, is directed to a mammal that is "asymptomatic to lung damage or wherein the clinical diagnosis of lung damage in said mammal cannot otherwise be confirmed without the aid of one or more invasive procedures." Similarly, the method claimed in the above-identified application, as currently recited in independent claim 57, is directed to a mammal that is "asymptomatic to alveolo-capillary membrane damage or wherein the clinical diagnosis of alveolo-capillary membrane damage in said mammal cannot otherwise be confirmed without the aid of one or more invasive procedures." That is, the methods of the pending claims do not cover just any mammal, but only those specifically recited mammals as articulated in the claims.

8. As would be understood by one of ordinary skill in the art, in determining an individual to be "asymptomatic" to lung damage or alveolo-capillary membrane damage, there is a relatively high degree of inquiry employed. The term "asymptomatic" denotes that a careful, observational assessment of the individual has been made by the clinician, typically including pertinent questions being asked by the clinician in the course of the clinician's evaluation of relevant criteria in assessing lung health. For example, the attached paper, Hankinson *et al.*, "Spirometric Reference Values from a Sample of the General U.S. Population," Am. J. Respir. Crit. Care Med. Vol. 159, pp. 179-187 (1999) ("Hankinson *et al.*"), describes the methodology underlying the development of now commonly cited reference equations for lung function. In Hankinson *et al.*, the included population is described as being "asymptomatic," and the detailed questioning that was

employed to confirm this "asymptomatic" status is described therein. *See* Hankinson *et al.*, p. 180, Tables 1 and 2; p. 181, col. 2, first full paragraph.

9. In the Office Action dated July 3, 2008, it states that "Doyle *et al.* compares OD (without evidence of cardiorespiratory disease) to normal levels. As such, they necessarily and inherently compared asymptomatic (i.e. without evidence of cardiorespiratory disease to normals)." (Office Action dated July 3, 2008, page 4). In the Office Action dated April 30, 2009, it states that "[n]o evidence of cardiorespiratory disease necessarily includes patient populations that are asymptomatic to lung damage or alveolo-capillary membrane damage without invasive procedures because they have *no evidence of cardiorespiratory disease*." (Office Action dated April 30, 2009, page 3 (emphasis in original)). One of ordinary skill in the art would not agree with these statements for at least the following reasons. Other published authors have labelled subjects as having "the absence of respiratory complaints," when in fact, subsequent enquiry established that they did have symptoms of cardiorespiratory disease and/or lung damage. As illustrated in the attached article by Martine Remy-Jardin *et al.*, "Morphologic Effects of Cigarette Smoking on Airways and Pulmonary Parenchyma in Healthy Adult Volunteers: CT Evaluation and Correlation with Pulmonary Function Tests," Radiology, Volume 186(1):107-115 (1993) ("Remy-Jardin *et al.*"), an individual could fall within the normal or OD groups of Doyle *et al.*, yet still not be within the scope of the patient populations of the pending claims. Remy-Jardin *et al.* discloses a study of 175 healthy adult volunteers, with no evidence of cardiorespiratory disease, separated into current smokers, ex-smokers and nonsmokers. *See* Remy-Jardin *et al.*, p. 107, col. 3 through p. 108, col. 1; and p. 112, col. 3. As can be seen in Table 2 of Remy-Jardin *et al.*, several of the healthy smokers were not asymptomatic to lung damage (*e.g.*, cough, wheezing, dyspnea present). As can be seen in Table 5 of Remy-Jardin *et al.*, several of the healthy smokers were diagnosed with emphysema via a high-resolution CT (HRCT) scan (*i.e.*, a non-invasive procedure). *See* Remy-Jardin *et al.*, Table 4; and p. 114, col. 2. Thus, the study of Remy-Jardin *et al.* could have included a healthy smoker with no evidence of cardiorespiratory disease, who was not asymptomatic to lung damage and who had lung damage (emphysema) which could be confirmed without the aid of an invasive procedure. If Doyle *et al.* had used the same criteria as Remy-Jardin, such an individual would be placeable within the normal or OD groups of Doyle *et al.*, yet not fall within the patient populations of the current claims.

10. In sum, upon reading Doyle *et al.*, one of ordinary skill in the art could not definitively determine the precise physical characteristics of the individuals in the normal group or OD group disclosed therein. That is, one of ordinary skill in the art could not determine with certainty that a member of the normal group or OD group disclosed therein is necessarily "asymptomatic to" lung damage or alveolo-capillary membrane damage, or necessarily of a condition that the clinical diagnosis of lung damage or alveolo-capillary membrane damage in the mammal "cannot otherwise be confirmed without the aid of one or more invasive procedures."

11. I hereby declare that all statements made herein to my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Respectfully submitted,

Guy B. Marks

28th May 2010

Date